American Journal of Medical Genetics 66:204–208 (1996)

Comprehensive 4-Year Follow-Up on a Case of Maternal Heterodisomy for Chromosome 16

Adele S. Schneider, Farideh Z. Bischoff, Christopher McCaskill, Mary Luz Coady, Jill E. Stopfer, and Lisa G. Shaffer

Department of Pediatrics, Albert Einstein Medical Center, Philadelphia (A.S.S., J.E.S.), Department of Pediatrics, Bryn Mawr Hospital and St. Christopher's Hospital for Children (M.L.C.), Philadelphia, Pennsylvania; and Department of Molecular and Human Genetics (F.Z.B., C.M., L.G.S.), Baylor College of Medicine, Houston, Texas

Uniparental disomy for chromosome 16 has been previously identified in fetal deaths and newborn infants with limited follow-up. Thus there is a lack of information about the long-term effects of maternal uniparental disomy 16 on growth and development. We present a case of maternal heterodisomy for chromosome 16 and a comprehensive 4-year physical and cognitive evaluation.

Cytogenetic analysis of chorionic villus obtained at 10 weeks gestation for advanced maternal age showed trisomy 16. At 15 weeks, amniocentesis demonstrated low level mosaicism 47,XY,+16[1]/46,XY[25]. Decreased fetal growth was noted in the last 2 months of pregnancy and the infant was small for gestational age at birth. Molecular studies revealed only maternal alleles for chromosome 16 in a peripheral blood sample from the child, consistent with maternal uniparental heterodisomy 16. Although short stature remains a concern, there appears to be no major cognitive effects of maternal disomy 16. Clinical evaluation and follow-up on additional cases should further clarify the role of placental mosaicism and maternal disomy 16 in intrauterine growth retardation and its effects on long-term growth in childhood.

KEY WORDS: intrauterine growth retardation (IUGR), uniparental disomy (UPD), confined placental mosaicism (CPM), short stature, chromosome 16

INTRODUCTION

Uniparental disomy (UPD) is the occurrence of both members of a chromosome pair, derived solely from one parent in a diploid offspring [Engel, 1980]. Although UPD was first hypothesized in 1980 [Engel, 1980], the first case in humans was not described until 1988 [Spence et al., 1988]. Since then, >50 cases of UPD have been described for more than half of the autosomes [reviewed in Ledbetter and Engel, 1995].

Aside from UPD 15 reported in Prader-Willi syndrome and Angelman syndrome, chromosome 16 is the most commonly reported example of UPD [Bennett et al., 1992; Dworniczak et al., 1992; Kalousek et al., 1993; Lindor et al., 1993; Vaughan et al., 1994; Whiteford et al., 1995]. This is likely due to the fact that trisomy 16 is the most common autosomal trisomy found in spontaneously aborted fetuses [Hassold and Jacobs, 1984] and probably the most common trisomy in conceptuses. Mosaic and nonmosaic trisomy 16 are also commonly identified during first trimester chorionic villus samplings (CVS) and most often reflect confined placental mosaicism (CPM) and not true fetal mosaicism [reviewed in Wolstenholme et al., 1995]. The "trisomy rescue" of an aneuploid conceptus, through loss of one of the extra chromosomes, would result in uniparental disomy one-third of the time. Since virtually all cases of trisomy 16 investigated to date have arisen through a maternal meiosis nondisjunction [Hassold et al., 1991], one would expect that most cases of UPD 16 would be maternal in origin. Indeed, all cases of UPD 16 reported to date are maternal disomy [Bennett et al., 1992; Dworniczak et al., 1992; Kalousek et al., 1993; Lindor et al., 1993; Vaughan et al., 1994; Whiteford et al., 1995].

The effects of maternal disomy 16 remain somewhat unclear. Cases of maternal disomy 16 reported to date have been in fetal deaths [Bennett et al., 1992; Kalousek et al., 1993; Vaughan et al., 1994] and newborn infants [Dworniczak et al., 1992; Kalousek et al., 1993; Whiteford et al., 1995] with the oldest documented case to be 11 months of age [Lindor et al., 1993]. A common phenotype to all cases is severe intrauterine growth retardation (IUGR). Additionally, many of the cases had some minor anomalies, such as clinodactyly,

Received for publication December 29, 1995; revision received March 12, 1996.

Address reprint requests to Lisa G. Shaffer, Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Room 15E, Houston, TX 77030.

or major anomalies, such as imperforate anus. Confounding the possible phenotypic effects of maternal disomy 16 is the presence of significant CPM in most of these pregnancies [Kalousek et al., 1993]. We report a comprehensive 4-year follow-up on a case of maternal heterodisomy 16.

CLINICAL REPORT

The patient is a 4-year-old white boy who was born at term to a 34-year-old G3P1011 mother. The pregnancy was complicated by intermittent hypertension, proteinuria, and edema in the last 4 weeks.

CVS was performed at 10 weeks of gestation for advanced maternal age. A chromosome complement of 47,XY,+16 was noted in all cells counted (n = 16) from cultured villi. The finding of an apparently normally growing fetus on ultrasound in association with trisomy 16 on CVS suggested a discrepancy between placental and fetal chromosomes since true trisomy 16 in a fetus would be expected to abort early in pregnancy. An amniocentesis at 15 weeks gestation demonstrated very low level mosaicism 47,XY,+16[1]/46,XY[25]. The pregnancy was closely monitored with ultrasound examinations, which showed decreased fetal growth in the last 2 months of pregnancy. Serial nonstress tests were negative.

The patient was born at term by spontaneous, vaginal delivery with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. At birth, he was noted to have hypospadias with chordee, IUGR with head sparing, mild left hydronephrosis, and 5th finger clinodactyly. His birth weight was 1,935 g (50th centile for 33 weeks gestation), birth length was 46 cm (50th centile for 35 weeks gestation), and head circumference was 10–25th centile for his gestational age of 38–39 weeks. He was discharged on day 5 of life.

Placental morphology was studied. The placenta was of normal size (18 cm × 17 cm × 4 cm), weighed 660 g, and was partially hemorrhagic. Sections from the hemorrhagic portion showed large areas of recent hematoma. A few neutrophils were noted in the chorion and umbilical cord, but not enough to constitute inflammation. Microscopy showed some hyalinization of villi throughout the placenta. A 3-vessel umbilical cord, eccentrically located, was present.

Chromosome studies on peripheral blood postnatally showed a normal 46,XY karyotype in all 58 cells studied. A skin biopsy was attempted but failed to grow in culture. Therefore, buccal cells were examined by fluorescence in situ hybridization (FISH) with an alpha-satellite probe specific for the centromere of chromosome 16 (Oncor). All 50 cells scored had two hybridization signals for the chromosome 16 probe.

The child has been followed for 4 years. His height and weight measurements are shown in Table I. Early catch-up growth occurred and by age 9 months, his weight and length were between the 10th and 25th centiles. Since age 20 months, his weight has dropped below the 3rd centile. His mother reports that he is a fussy eater. His head has grown consistently above the 50th centile.

TABLE I. Growth Parameters During 4-Year Period for Child With Maternal Heterodisomy 16

Age (months)	Weight (kg)	Length (cm)
Birth	1.935 (<3%ile)	46.0 (<3%ile)
3	4.8 (10%ile)	55.5 (<3%ile)
6	6.5 (10%ile)	64.0 (5%ile)
8	7.9 (10–25%ile)	68.5 (5–10%ile)
10	8.5 (10%ile)	73.0 (25%ile)
12	8.8 (5–10%ile)	74.5 (25%ile)
18	9.4 (<3%ile)	77.0 (5%ile)
24	10 (<3%ile)	83.8 (10%ile)
36	12 (<3%ile)	91.4 (5%ile)
48	13.6 (5%ile)	96.5 (5–10%ile)

Surgical correction of the hypospadias was performed at 9 months without complications. The hydronephrosis has resolved. This is a child with minor anomalies (Fig. 1) whose development was assessed at age 36 months using the Hawaii Early Learning Profile (HELP) [Parks, 1992] and Receptive Expressive Emergent Language-2 (REEL-2) [Bzoch and League, 1991]. He tested in the average range in all areas with strengths in fine motor skills and receptive and expressive language. He is an active and sociable child who is in good general health.

MOLECULAR ANALYSES

DNA was extracted from peripheral blood from the mother, father, and child by standard procedures. DNA was extracted from a formalin-fixed placental sample by the methods of Schubert et al. [1993]. Molecular analysis was performed using previously published methods [Shaffer et al., 1993] with the following modifications. Four dinucleotide repeat markers specific for chromosome 16 (D16S296, D16S291, D16S285, HBAP1) were used to identify the parental origins of the chromosomes 16 in the child. The primer sequence information was obtained through the Genome Data Base and the primers were synthesized by the sequencing core within the Department of Molecular and Human Genetics at Baylor College of Medicine. Heterozygosities for these markers range from 0.73 to 0.83. Two nonchromosome 16 markers (D13S119 and D13S121) were used to assess paternity [Bowcock et al., 1993]. For each amplification, 0.1 μM of primer was used.

Molecular analysis of the patient's genomic DNA demonstrated alleles of only maternal origin and lack of inheritance of any paternal allele for all chromosome 16 markers tested (Fig. 2, Table II). The placental DNA allele pattern was consistent with the inheritance of both maternal chromosomes 16 and one paternal chromosome 16. For markers D16S285 and HBAP1, the child inherited both maternal alleles, consistent with maternal heterodisomy. For these markers, the placenta inherited both maternal alleles and one paternal allele, consistent with two copies of chromosome 16 from the mother and the trisomy 16 seen by chromosome analysis of the CVS. For each chromosome 13 marker, the child and placenta show the same normal biparental inheritance pattern consistent with correct paternity (Fig. 2) (Table II).

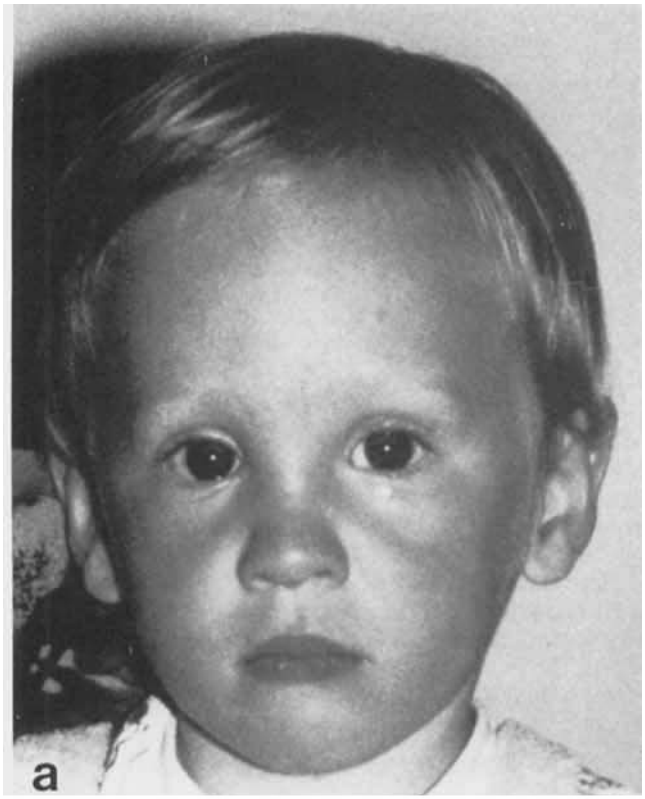

Fig. 1. Propositus at age (**a**) 20 months and (**b**) 36 months.

DISCUSSION

The results of only maternal alleles and heterozygosity at the D16S285 and HBAP1 loci in the child are consistent with maternal heterodisomy 16. However, isodisomy due to recombination cannot be excluded at other chromosome 16 loci. These results suggest an initial maternal meiosis I nondisjunction event leading to a trisomy 16 conceptus and subsequent loss of the paternal chromosome 16 resulting in maternal heterodisomy in the fetus. This mechanism may be the most common mechanism giving rise to UPD and has been reported previously for several cases including UPD 15 [Purvis-Smith et al., 1992; Cassidy et al., 1992], UPD 10 [Jones et al., 1995], and UPD 16 [Kalousek et al., 1993].

The clinical findings in cases with maternal disomy 16 may be due to: (1) imprinting effects, (2) high levels of trisomic cells in the placenta, (3) undetected mosaicism for trisomy 16 in the individual, and (4) recessive disease due to isodisomy. The IUGR associated with these cases appears to be due to the high level of CPM found [Kalousek et al., 1991; Kalousek and Barrett, 1995] and perhaps this plays a role in placental dysfunction. Previous cases of maternal disomy 16 have reported placentas with hematomas [Bennett et al., 1992], fibrinous deposition, areas of microinfarctation, and two vessel cords [Vaughan et al., 1994; Whiteford et al., 1995]. It is unclear if the histologic abnormalities seen in the placenta of our patient contributed to his IUGR.

Cases of maternal disomy 16 have exhibited a wide range of phenotypes. Some cases have resulted in fetal demise or neonatal death [Bennett et al., 1992; Kalousek et al., 1993; Vaughan et al., 1994; Whiteford et al., 1995; Shaffer, unpub.]. All of these cases had IUGR and some had major anomalies including imperforate anus [Kalousek et al., 1993; Vaughan et al., 1994]. Other cases have shown some minor anomalies, including inguinal hernias [Dworniczak et al., 1992; Whiteford et al., 1995], hypospadius [Kalousek et al., 1993; Whiteford et al., 1995; current case], and clinodactyly [Whiteford et al., 1995; current case]. Hypospadius has been observed in infants with mosaic trisomy 16 but is usually associated with other severe anomalies [Pletcher et al., 1994]. Although not completely excluded, cytogenetic studies of peripheral blood and buccal cells failed to demonstrate any trisomy 16 cells in the current case. Isolated hypospadius has an incidence of 3.9–20.1 per 10,000 live born males [reviewed in Avellán, 1975] and is therefore relatively common. A multifactorial mode of inheritance has been postulated [Emery and Rimoin, 1983]. Likewise, clinodactyly of the 5th finger has been estimated to be in 1–19.5% of the general population [Burke and Flatt, 1979; Skvarilova and Smahel, 1984]. Therefore, it remains possible that these minor anomalies are not associated with the maternal disomy 16 and are sporadic occurrences in this patient.

The propositus in the current case is demonstrating some catch-up growth, although at 4 years of age, his height is less than the 10th percentile. The parental

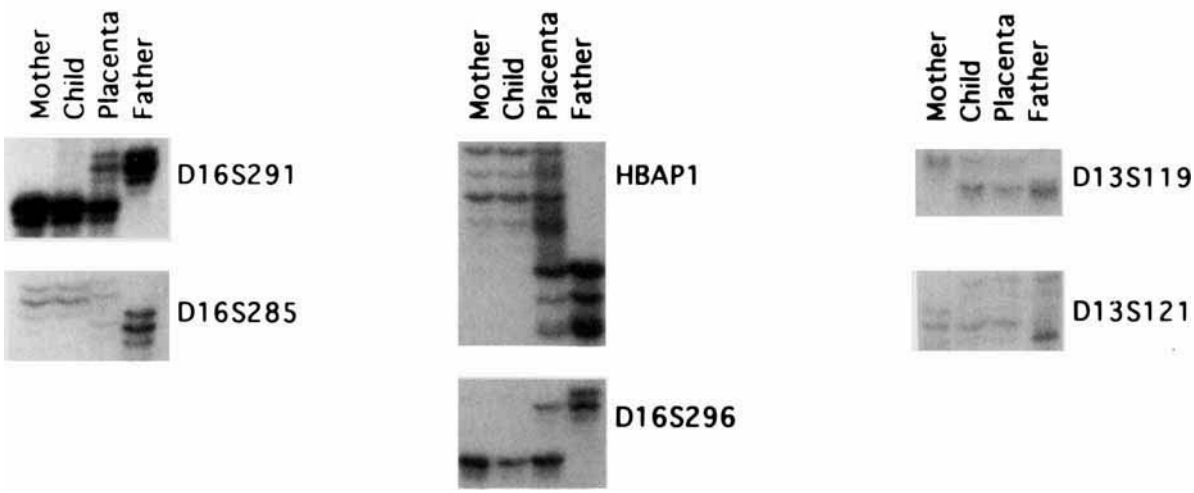

Fig. 2. Molecular results for chromosome 16 and 13 markers. For each chromosome 16 marker, the child inherited only maternal alleles. The placenta sample shows inheritance of a paternal allele in addition to two maternal alleles for D16S285 and HBAP1. This would be consistent with a "trisomy rescue" resulting in uniparental disomy in the child. Note that in the placental lanes for markers D16S291 and HBAP1, "shadow" bands and some smearing are evident. This tends to be more apparent for certain markers and most likely is due to the extraction of poor quality, perhaps partially degraded DNA from the formalin-fixed placental tissue.

TABLE II. Molecular Results for Child and Placenta for Chromosomes 16 and 13 Loci*

						Interpretation[a]	
Locus	Location	M	C	P	F	C	P
D16S291	16p13.3	3,3	3,3	2,3	1,2	MD	BPD
D16S285	16q12.1	1,2	1,2	1,2,4	3,4	MD	MT[b]
HBAP1	16p13.3	1,2	1,2	1,2,3	3,3	MD	MT[b]
D16S296	16p12.3	3,3	3,3	2,3	1,2	MD	BPD
D13S119	13q14.3–q22	1,1	1,3	1,3	2,3	BPD	BPD
D13S121	13q31	2,3	1,3	1,3	1,4	BPD	BPD

*Alleles are shown for mother (M), child (C), placenta (P) and father (F), respectively.
[a]MD=maternal disomy, BPD=normal biparental disomy, MT=trisomy of maternal origin.
[b]Three distinct alleles in the placenta indicate a meiotic origin of the trisomy.

heights are within normal limits at 5 ft, 3.5 inches for the mother and 5 ft, 9.5 inches for the father.

Limited follow-up has been previously presented for two cases of maternal disomy 16; one at 3 months of age [Dworniczak et al., 1992] and one at 11 months of age [Lindor et al., 1993]. Reportedly, both patients showed adequate growth at their respective ages. One possibility for the current case is that the short stature is due to undetected mosaic trisomy 16. However, Lindor et al. [1993] had documented mosaic trisomy 16 in the skin of a patient who was at the 10th centile for growth at 10 months of age. An additional cause of the short stature may be genomic imprinting at some loci on chromosome 16. Genomic imprinting has been implicated in the short stature seen with maternal disomy 7 [Voss et al., 1989; Spotila et al., 1992; Höglund et al., 1994; Kotzot et al., 1995].

Discrepant cytogenetic results between CVS and amniocentesis warrants further molecular evaluation for UPD. Based on the current case, the finding of maternal heterodisomy 16 offers an optimistic outlook for the child's early intellectual development. Continued follow-up is needed to assess any long-term effects of maternal disomy for chromosome 16 on the ultimate growth and development of these children.

REFERENCES

Avellán L (1975): The incidence of hypospadias in Sweden. Scand J Plast Reconstr Surg 9:129–139.

Bennett P, Vaughan J, Henderson D, Loughna S, Moore G (1992): Association between confined placental trisomy, fetal uniparental disomy, and early intrauterine growth retardation. Lancet 340:1284–1285.

Bowcock A, Osborne-Lawrence S, Barnes R, Chakravarti A, Washington S, Dunn C (1993): Microsatellite polymorphism linkage map of human chromosome 13q. Genomics 15:376–386.

Burke F, Flatt A (1979): Clinodactyly. A review of a series of cases. Hand 11:269–280.

Bzoch K, League R (1991): Receptive-Expressive Emergent Language Scale, 2nd ed, (REEL-2), PRO-ED, Austin, TX.

Cassidy SB, Li-Wen L, Erickson RP, Magnuson L, Thomas E, Gendron R, Herrmann J (1992): Trisomy 15 with loss of the paternal 15 as a cause of Prader-Willi syndrome due to maternal disomy. Am J Hum Genet 51:701–708.

Dworniczak B, Koppers B, Kurlemann G, Holzgreve W, Horst J, Miny P (1992): Uniparental disomy with normal phenotype. Lancet 340:1285.

Emery AEH, Rimoin DL (1983): "Principles and Practice of Medical Genetics." New York: Churchill Livingstone, p 1431.

Engel E (1980): A new genetic concept: Uniparental disomy and its potential effect, isodisomy. Am J Med Genet 6:137–143.

Hassold TJ, Pettay D, Freeman SB, Grantham M, Takaesu N (1991): Molecular studies of non-disjunction in trisomy 16. J Med Genet 28:159–162.

Hassold TJ, Jacobs PA (1984): Trisomy in man. Ann Rev Genet 18: 69–97.

Höglund PN, Holmberg C, de la Chapelle A, Kere J (1994): Paternal isodisomy for chromosome 7 is compatible with normal growth and development in a patient with congenital chloride diarrhea. Am J Hum Genet 55:747–752.

Jones C, Booth C, Rita D, Jazmines L, Spiro R, McCulloch B, McCaskill C, Shaffer LG (1995): Identification of a case of maternal uniparental disomy of chromosome 10 associated with confined placental mosaicism. Prenat Diagn 15:843–848.

Kalousek DK, Barrett I (1994): Genomic imprinting related to prenatal diagnosis. Prenat Diagn 14:1191–1201.

Kalousek DK, Langlois S, Barrett I, Yam I, Wilson DR, Howard-Peebles PN, Johnson MP, Giorgiutti E (1993): Uniparental disomy for chromosome 16 in humans. Am J Hum Genet 52:8–16.

Kalousek DK, Howard-Peebles PN, Olson SB, Barrett IJ, Dorfmann A, Black SH, Schulman JD, Wilson RD (1991): Confirmation of CVS mosaicism in term placentae and high frequency of intrauterine growth retardation association with confined placental mosaicism. Prenat Diagn 11:743–750.

Kotzot D, Schmitt S, Bernasconi F, Robinson WP, Lurie IW, Ilyina H, Méhes K, Hamel BCJ, Otten BJ, Hergersberg M, Werder E, Schoenle E, Schinzel A (1995): Uniparental disomy 7 in Silver-Russell syndrome and primordial growth retardation. Hum Mol Genet 4:583–587.

Ledbetter DH, Engel E (1995): Uniparental disomy in humans: development of an imprinting map and its implications for prenatal diagnosis. Hum Molec Genet 4:1757–1764.

Lindor NM, Jalal SM, Thibodeau SN, Bonde D, Sauser KL, Karnes PS (1993): Mosaic trisomy 16 in a thriving infant; maternal heterodisomy for chromosome 16. Clin Genet 44:185–189.

Parks S (1992): Hawaii Early Learning Profile (HELP). Vort Corp., Palo Alto, CA.

Pletcher BA, Sanz MM, Schlessel JS, Kunaporn S, McKenna C, Bialer MG, Alonso ML, Zaslav A-L, Brown WT, Ray JH (1994): Postnatal confirmation of prenatally diagnosed trisomy 16 mosaicism in two phenotypically abnormal liveborns. Prenat Diagn 14:933–940.

Purvis-Smith SG, Saville T, Manass S, Yip M-Y, Lam-Po-Tang PRL, Duffy B, Johnston H, Leigh D, McDonald B (1992): Uniparental disomy 15 resulting from "correction" of an initial trisomy 15. Am J Hum Genet 50:1348–1350.

Schubert EL, Bischoff FZ, Whitaker LL, Pheasants LM, Hansen MF (1993): A method to isolate DNA from small archival tissue samples for p53 gene analysis. Hum Mutat 2:123–126.

Shaffer LG, Overhauser J, Jackson L, Ledbetter DH (1993): Genetic syndromes and uniparental disomy: A study of 16 cases of Brachmann-de Lange syndrome. Am J Med Genet 47:383–386.

Skvarilova B, Smahel Z (1984): Clinodactyly-frequency and morphological implications. Acta Chirurgiae Plasticae 26:72–78.

Spence JE, Perciaccante RG, Greig GM, Willard HF, Ledbetter DH, Hejtmancik JF, Pollack MS, O'Brien WE, Beaudet AL (1988): Uniparental disomy as a mechanism for human genetic disease. Am J Hum Genet 42:217–226.

Spotila LD, Sereda L, Prockop DJ (1992): Partial isodisomy for maternal chromosome 7 and short stature in an individual with a mutation at the COL1A2 locus. Am J Hum Genet 51:1396–1405.

Vaughan J, Ali Z, Bower S, Bennett P, Chard T, Moore G (1994): Human maternal uniparental disomy for chromosome 16 and fetal development. Prenat Diagn 14:751–756.

Voss R, Ben-Simon E, Avital A, Godfrey S, Zlotogora J, Dagan J, Tikochinski Y, Hillel J (1989) Isodisomy of chromosome 7 in a patient with cystic fibrosis: Could uniparental disomy be common in humans? Am J Hum Genet 45:373–380.

Whiteford ML, Coutts J, Al-Roomi L, Mather A, Lowther G, Cooke A, Vaughan JI, Moore GE, Tolmie JL (1995): Uniparental isodisomy for chromosome 16 in a growth-retarded infant with congenital heart disease. Prenat Diagn 15:579–584.

Wolstenholme J (1995): An audit of trisomy 16 in man. Prenat Diagn 15:109–121.